Non-steroidal anti-inflammatory drug-induced enteropathy as a major risk factor for small bowel bleeding

Doo-Ho Lim
Ulsan University Hospital
Kyoungwon Jung
Kosin University Gospel Hospital
Seung Bum Lee (sblee@uuh.ulsan.kr)
Ulsan University Hospital https://orcid.org/0000-0002-5880-5659
In Kyu Park
Ulsan University Hospital
Hee Jeong Cha
Ulsan University Hospital
Jae Ho Park
Ulsan University Hospital
Byung Gyu Kim
Ulsan University Hospital
Seok Won Jung
Ulsan University Hospital
In Du Jeong
Ulsan University Hospital
Jae Hyun Kim
Kosin University Gospel Hospital
Sung Eun Kim
Kosin University Gospel Hospital
Won Moon
Kosin University Gospel Hospital
Moo In Park
Kosin University Gospel Hospital
Seun Ja Park
Kosin University Gospel Hospital

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Abstract

Background: Small bowel (SB) bleeding has been known to account for 5% of all gastrointestinal (GI) bleeding cases and 80% of obscure GI bleeding cases. Although angioectasia is the common etiology of SB bleeding, non-steroidal anti-inflammatory drug (NSAID)-induced SB lesion is also reported as a major cause in previous studies from the Eastern countries. Herein, we assessed the frequency of NSAID-induced SB lesion in Korean patients with obscure GI bleeding.

Methods: We retrospectively analyzed medical records of all consecutive patients aged ≥18 years who underwent capsule endoscopy from March 2018 to February 2019 at Ulsan University Hospital and Kosin University Gospel Hospital.

Results: Of the 83 subjects (age, mean ± standard deviation: 59 ± 18 years; age range: 18–84 years; men, n=52; women, n=31), 55 (66.2%) had a clear bloody stool and 28 (33.8%) had a normal stool, but all had iron deficiency anemia. A significantly higher frequency (40 of 51) of ulcerative/erosive lesions was observed in patients with inactive bleeding but visible SB lesions than other causes, and as a result, NSAID-induced enteropathy accounted for 41.7% (25 of 60) of all SB bleeding cases.

Conclusions: Contrary to findings of previous studies from the Western countries, ulcerative/erosive lesions were found to have higher occurrence than angioectasia in this study, with an implication of NSAIDs in the etiology of obscure GI bleeding. Aggressive small intestine examination is required for patients with unexplained GI bleeding.

Background

Obscure gastrointestinal (GI) bleeding has been defined as persistent or recurrent bleeding of unknown origin despite of repetitive diagnostic studies, including upper GI endoscopy and colonoscopy.[1] Small bowel (SB) bleeding has been known to account for 80% of obscure GI bleeding cases and 5% of all GI bleeding cases. Unexplained iron deficiency anemia is a common manifestation of obscure GI bleeding in 30–40% of cases.[2] Capsule endoscopy is the first-line examination in obscure GI bleeding, whereas in cases of ongoing overt bleeding, this procedure is recommended as the next diagnostic test after negative upper and lower endoscopy results.[3–6] Angioectasia is the most common etiology of SB bleeding in the Western countries,[4, 7, 8] while non-steroidal anti-inflammatory drug (NSAID)-induced SB lesion is the major cause reported in Japanese studies.[9, 10]

NSAIDs are widely prescribed in most clinical conditions, but these drugs are well known to cause GI complications.[11] Although various studies have reported an association between NSAID intake and GI adverse effects,[12, 13] the role of NSAIDs in small intestinal bleeding remains to be elucidated. Therefore, we aimed to assess the frequency of NSAID-induced SB lesions in Korean patients with obscure GI bleeding who underwent capsule endoscopy.

Methods

Study population

We retrospectively evaluated medical records of all consecutive patients aged ≥18 years with obscure GI bleeding who underwent capsule endoscopy from March 2018 to February 2019 at our two medical institutions, Ulsan University Hospital and Kosin University Gospel Hospital. Indication for the test included bloody stool in patients with unidentified bleeding lesions during diagnostic evaluations, including the upper GI endoscopy, colonoscopy, and abdominal computed tomography (CT) in the last 3 months.[5] We also included patients who had no visible bloody stool, showed persistent or repeated exacerbation of iron deficiency anemia despite iron supplement for >6 months, and no hemorrhagic lesions identified during the above screening methods in the last 3 months.[14] Rebleeding was defined as recurrent anemia (≥2 g/dL decrease in hemoglobin level), overt melena/ hematochezia or occult GI bleeding during the follow-up period.[15] This study was approved by the Institutional Review Board (IRB, the local ethical committee) of the Ulsan University Hospital (IRB No. 2019-10-014) and the Kosin University Gospel Hospital (IRB No. 2019-10-001). The requirement for informed consent of patients was waived by IRB because patient records and information were de-identified prior to analysis.

Capsule endoscopy

Capsule endoscopy was performed using Pillcam® (Given Imaging Ltd., Yoqneam, Israel) and MiroCam® (IntroMedic Ltd., Seoul, Korea) devices. All patients underwent fasting for 12 hours and received 40 mg oral simethicone before the procedure to prevent air-bubble formation.[16] Moreover, we used 2L polyethylene glycol solution before examination for the improved image quality of SB.[17] Five gastroenterologists with extensive GI endoscopic experience reviewed all capsule video images. All images were extensively discussed to reach a diagnosis.

Ulcerative lesions were defined as mucosal penetrating lesions with diameters > 5 mm.[15] An erosion was a roundish area of mucosal disruption smaller than 5 mm of diameters.[18] The etiology of ulcerated lesions was determined based on clinical information and endoscopic findings. We examined NSAID-induced enteropathy based on the systematic review of criteria[12] as (1) history of NSAIDs use; (2) endoscopic findings, ulcers and erosions, including scar change or luminal stenosis; (3) improvement of clinical course and/or endoscopic findings after cessation of NSAIDs; and (4) exclusion of other etiologies, including infection, inflammatory bowel disease or malignancy.

Statistical analysis

Continuous variables were compared using Student's *t*-test, and categorical variables were analyzed with chi-square or Fisher's exact test. A two-tailed p-value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS statistical package for Windows, Version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Sample analysis

We assessed 83 subjects who underwent capsule endoscopy during the study period (age, mean ± standard deviation: 59 ± 18 years; age range: 18–84 years; men, n = 52; women, n = 31; Table 1). Of these, 55 (66.2%) patients had a clear bloody stool and 28 (33.8%) had a normal stool, all with iron deficiency anemia (Figure 1). Among 37 (44.6%) patients with a history of low-dose aspirin or NSAID medication, only three treated with selective cyclooxygenase (COX)–2 inhibitors showed a normal stool. The majority of patients with active bleeding during endoscopy had angioectasia (8 of 9 patients). Fecal occult blood test, performed in patients with normal stools (16 of 28), was negative in 12 patients, among which 7 had no SB lesions. A significantly higher frequency (40 of 51) of ulcerative/erosive lesions was observed in patients with inactive bleeding but visible SB lesions than other causes, among whom 62.5% (25 of 40) had a history of low-dose aspirin or NSAID medication. As a result, NSAID-induced enteropathy accounted for 41.7% (25 of 60) of all SB bleeding cases. Five cases of previously undiagnosed Crohn's disease were identified. Other uncommon etiologies associated with unknown GI bleeding included radiation ileitis (n = 3) and SB polyps (n = 3).

Evaluation of rebleeding and treatment

During capsule endoscopy, 58 (69.9%) patients had anemia with hemoglobin <10 g/dL. SB bleeding was predominant in >50% (17 of 28) of patients with normal stool. All patients with SB bleeding due to angioectasia showed bloody stools, while ulcerative lesions were prevalent in patients with normal stool. Rebleeding occurred in 9 patients during the 6-month follow-up period. All patients with Crohn's disease (n = 5) who presented with persistent iron deficiency anemia required specific biologic treatments. Among two patients with radiation ileitis, one underwent surgical treatment due to recurrent bloody stool, whereas the other patient with persistent iron deficiency anemia refused an SB resection. A patient with a rebleeding episode from angioectasia received angiographic embolization. In our patient samples, a 65-year-old woman, who received NSAIDs for treating fibromyalgia for >2 years, presented with an ulcerative lesion. The patient had unresolved anemia despite adequate iron administration and showed recurrent abdominal pain, which lasted for >6 months. An abdominal CT revealed multiple strictures of the SB. During the procedure, when the capsule failed to pass through the site, the retained capsule was retrieved through a surgical resection, which identified five sites of stenosis in the distal ileum. Postoperative 3-month follow-up revealed no recurrence of anemia and abdominal pain (Figure 2).

Discussion

A diagnostic yield of 57–62% have been reported with capsule endoscopy for unexplained GI bleeding,[19] with the most common diagnosis of angioectasia (50%), followed by ulcers (26.8%) and tumors (8.8%), as suggested by a recent systematic literature review.[14] The present study revealed that the detection rate of SB bleeding and lesion in capsule endoscopy was 72.3% (60 of 83 patients) for obscure GI bleeding, in which, NSAID-induced enteropathy accounted for 41.7% (25 of 60) of all SB bleeding cases. Contrary to previous reports from the Western countries, we observed a higher occurrence rate of ulcerative/erosive lesions than angioectasia in our Korean patients with obscure GI bleeding, showing the implication of low-dose aspirin or NSAID medications in the disease etiology.

NSAIDs are frequently used anti-inflammatory analgesic agents that represent 7.7% of worldwide prescriptions, of which 90% are prescribed to elderly (>65 years) patients.[20] The mechanism of NSAID-induced enteropathy is supposed to be mediated through COX inhibition.[21] Administration of low-dose aspirin (irreversible nonselective COX inhibitor) is also associated with a SB mucosal injuries; taking of low-dose enteric-coated aspirin at 100 mg in healthy volunteers reported large erosions or ulcers in 60% of these participants.[22, 23] In the present study, a history of low-dose aspirin or NSAID medications was common in patients with obscure GI bleeding (44.6%), showing a higher frequency of SB ulcerative lesions (68%) than that of other sources of lesions (angioectasia, n = 6; upper or lower GI bleeding, n = 6).

Prostaglandins (PG) play an important role in regulating GI blood flow and mucus production; therefore, NSAID-induced suppression of PG production has been implicated in small intestinal damage.[24, 25] Previously, COX–1 inhibition was regarded to be dominantly related with GI mucosal injuries. However, in a recent animal model study, small intestinal damage developed only when both COX–1 and COX–2 were prohibited.[26] This result indicates that COX–2-derived PGs also play an important role in the maintenance of tissue integrity and repairing of mucosal injury. However, clinical research has shown conflicting results. Several studies showed an improved GI safety profile with selective COX–2 inhibitors compared to non-selective NSAIDs,[27, 28] while others studies indicated no significant differences in SB injuries between these NSAIDs.[29, 30] In this study, among 37 patients with a history of low-dose aspirin or NSAID medications, all three patients treated with the selective COX–2 inhibitors showed a normal stool, suggesting favorable GI safety outcomes of selective COX–2 inhibitor therapy. Considering selective COX–2 inhibitors are not completely safe for the SB, further long-term studies with a larger sample size are warranted to establish the safety profile of the drug in the SB.

Furthermore, the impact of capsule endoscopy on clinical outcomes remains controversial despite reports of SB mucosal damage in 70% of patients taking NSAIDs,[31, 32] because it remains unclear whether SB mucosal injuries contribute to significant bleeding.[33] Although patients with NSAID-induced SB injury show low frequency of severe bleeding in the SB,[34] rebleeding rates of 21–35% has been reported in patients with SB ulcerations during a mean follow-up period of 17.1–29.7 months.[15, 35] These reports suggest the clinical implication of SB ulcers, which cannot be ignored.

The most effective method of preventing NSAID-induced enteropathy is discontinuation of NSAIDs if it is possible.[12] Until recently, there are no definite strategy to prevent NSAID-induced enteropathy.[13, 36] A recent study reported the effectiveness of misoprostol in the treatment of SB ulcer bleeding associated with aspirin.[37] On the contrary, lesions inducing stenosis, which may not be treated with medication alone, require endoscopic or surgical interventions.[38] In this present study, a patient suffering from fibromyalgia developed SB stricture after NSAID medications for >2 years and eventually underwent surgical resection.

This present study has several limitations. First, it was a retrospective analysis with a small sample size that had a low statistical power to detect a significant effect. Second, because balloon-assisted enteroscopy was not routinely performed, pathological findings could not confirm SB ulcers. Third, the short follow-up period prevented the adequate assessment of risk factors for rebleeding. Finally, the fecal occult blood test could not be performed in approximately 50% (12 of 28) of patients who presented with normal stools, thereby limiting the interpretation of the results.

Conclusions

This study showed an improved diagnostic yield of capsule endoscopy for obscure GI bleeding and reaffirmed that NSAID-induced enteropathy is the most common etiology of SB bleeding in the Eastern populations, contrary to reports from the Western countries. Therefore, aggressive clinical management, including SB capsule endoscopy, should be considered for patients with unexplained GI bleeding or drug-refractory iron deficiency anemia, particularly during aspirin or NSAID medications.

Declarations

Abbreviations

GI, gastrointestinal; SB, small bowel; NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; PG, prostaglandin; CT, computed tomography

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Not Applicable.

Author contributions

Study coordination and drafting of the manuscript: DHL and KJ. Study coordination and critical review of the manuscript: DHL and LSB. Review of capsule endoscopy images: KJ, LSB, JHP, JHK, and SEK. Data supply and approval of the final version of this manuscript: IKP, HJC, BGK, IDJ, and MW. Data analysis and approval of the final version of this manuscript: SWJ, MIP, and SJP. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB, the local ethical committee) of the Ulsan University Hospital (IRB No. 2019-10-014) and the Kosin University Gospel Hospital (IRB No. 2019-10-001).

Consent for publication

The requirement for informed consent of patients was waived by IRB because patient records and information were de-identified prior to analysis.

Competing interests

The authors declare no competing interests.

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Table

Table 1. Clinical characteristics of patients

Characteristics	Overall (n=83)	Bloody stool (n=55)	Normal stool (n=28)	p-value
Age, yr	59 ± 18	61 ± 19	56 ± 15	0.185
Sex, male	52 (62.7)	37 (67.3)	15 (53.6)	0.222
Aspirin/NSAID	37 (44.6)	25 (45.5)	12 (42.9)	0.822
Hemoglobin (g/dL)	8.7 ± 3.0	8.7 ± 2.8	8.9 ± 3.5	0.785
Albumin (g/dL)	3.8 ± 0.6	3.7 ± 0.7	3.9 ± 0.6	0.191
Small bowel bleeding	60 (72.3)	43 (78.2)	17 (60.7)	0.093
Specific lesion*				
Angioectasia	14 (23.3)	14 (32.6)	0 (0.0)	
NSAID-induced enteropathy	25 (41.7)	15 (34.9)	10 (58.8)	0.024
Other causes†	21 (35.0)	14 (32.6)	7 (41.2)	
Site of bleeding*				
Jejunum	16 (26.7)	14 (36.2)	2 (11.8)	
Ileum	38 (63.3)	26 (60.5)	12 (70.6)	0.169
Indeterminate	6 (10.0)	3 (7.0)	3 (17.6)	
Rebleeding in 6 months*				
Yes	9 (15.0)	6 (14.0)	3 (17.6)	
No	48 (80.0)	34 (79.1)	14 (82.4)	0.519
Unknown	3 (5.0)	3 (7.0)	0 (0.0)	

*The denominator is 60 patients with confirmed small bowel lesion.
†Other causes of small bowel bleeding, including Crohn’s disease, radiation ileitis, small bowel polyps, and small bowel lesion with unknown causes.
Categorical and continuous variables are presented as number (%) and mean ± SD, respectively. Abbreviations: SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; Hb, hemoglobin.

Figures

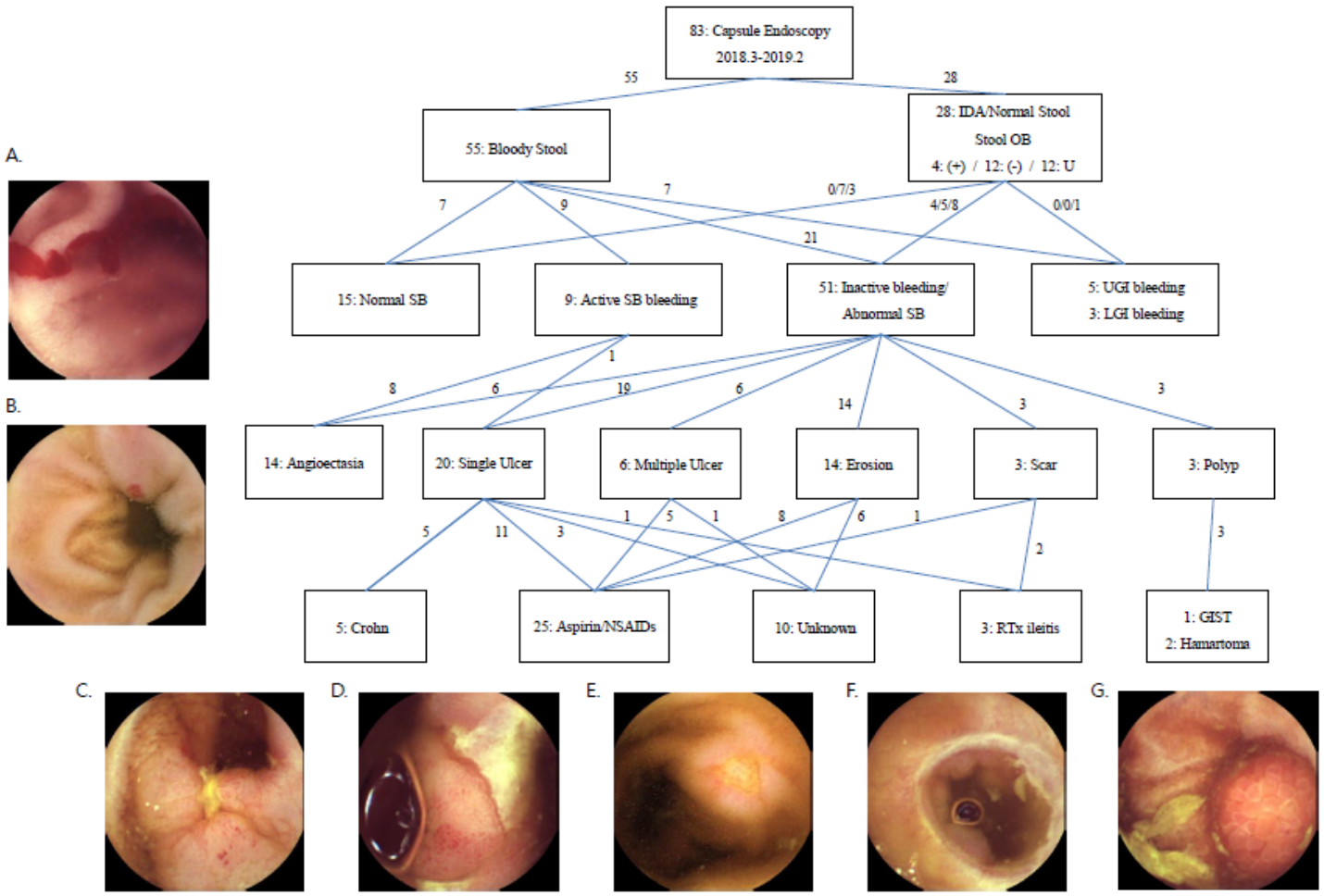

Figure 1

Representative capsule endoscopy images of small bowel lesions. A. Angioectasia with active bleeding. B. Angioectasia with no bleeding. C. Crohn's disease. D. NSAID-induced enteropathy (ulcer). E. NSAID-induced enteropathy (erosion). F. Radiation ileitis. G. SB polyp (GIST). IDA, iron deficiency anemia; OB, occult blood; SB, small bowel; UGI, upper gastrointestinal; LGI, lower gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; RTx, radiotherapy; GIST, gastrointestinal stromal tumor.

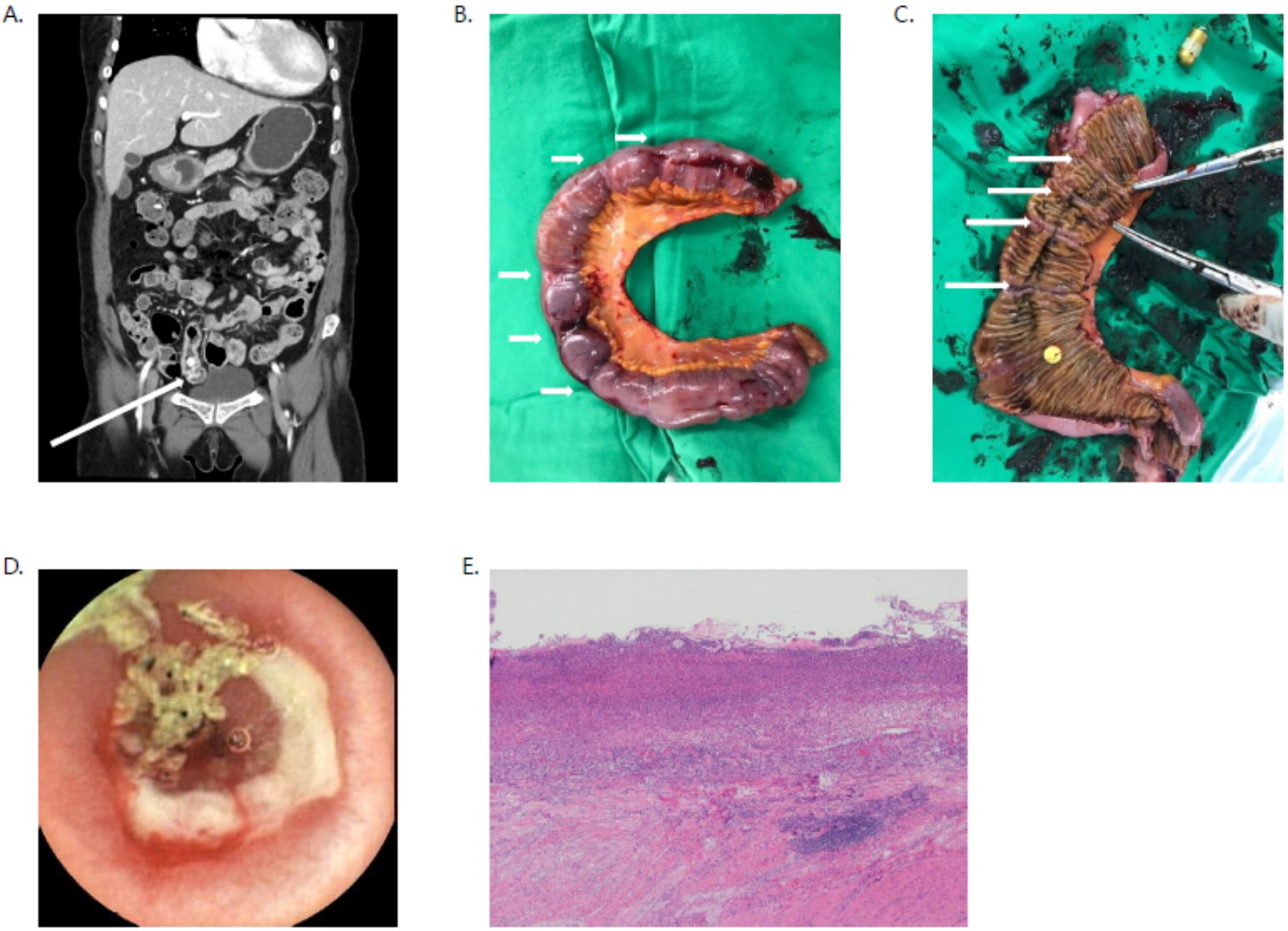

Figure 2

Surgical intervention in a patient with small-bowel stricture. A. Abdominal computed tomography showing stricture in the distal ileum. B. Gross findings after bowel resection with multiple stricture sites. C. Surgical resection exposing the inside of the small intestine. D. Capsule endoscopy image showing semi-circular ulcer with active hemorrhage. E. Histologic findings show ulceration including diffuse loss of villi, mucosal and submucosal neutrophilic exudates and transmural inflammation (Hematoxylin and Eosin x40).